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10/565,903	06/21/2006	Alessandro Massimo Gianni	3765-0119US1	7353

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EXAMINER	
NIEBAUER, RONALD T	
ART UNIT	PAPER NUMBER
1654	

NOTIFICATION DATE	DELIVERY MODE
09/18/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

mailroom@bskb.com

Office Action Summary	Application No.	Applicant(s)	
	10/565,903	GIANNI ET AL.	
	Examiner	Art Unit	
	RONALD T. NIEBAUER	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 May 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *27-36* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *27-36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 5/28/08 has been entered.

Applicants amendments and arguments filed 5/28/08 are acknowledged and have been fully considered. Any rejection and/or objection not specifically addressed is herein withdrawn.

Claims 1-26 have been canceled. Claims 27-36 have been added.

Claims 27-36 are under consideration.

Claim Objections

Claim 32 is objected to because of the following informalities:

claim 32 recites 'by parenteral route'. The word 'a' appears to be missing after the word 'by'.

Appropriate correction is required.

Specification

The disclosure is objected to because of the following informalities:

37 CFR 1.52 (b)(5) states 'the pages of the specification including claims and abstract must be numbered consecutively, starting with 1, the numbers being centrally located above or preferably below, the text'. In the instant case, the first page of the specification is not numbered.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 30-36 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 30 and dependent claims recite '..comprising the sole step of administering either separately or simultaneously..'. It is unclear how separate administrations could be considered a sole step. If agents are administered separately there are necessarily at least 2 steps: the administration of the first agent followed by the administration of the second agent. Claim 36 states that the agents may be administered 'sequentially'. Sequential administration necessarily requires at least 2 steps: the administration of the agent followed in sequence by another administration. As claimed, it is unclear what the term 'sole step' means in context of the instant claims. Further, it is noted that the phrase 'comprising' is inclusive or open-ended and does not exclude additional method steps (MPEP section 2111.03). As such, the phrase 'comprising the sole step' is unclear as to whether or not the phrase is to be interpreted as open to additional steps

or if the phrase is to be interpreted like the phrase 'consisting of' which excludes any element, step, or ingredient no specified in the claim.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 27-30,32-36 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 27-29 and drawn to compositions that consist essentially of an association of granulocyte colony stimulating factor and placental growth factor. Claims 30-36 are drawn to specific methods for patients in need of particular treatments.

Although unclear (see 112 2nd) for purposes of examination, claims 30-36 have been interpreted such that the claims are inclusive or open-ended and do not exclude additional method steps.

Lack of Ipsis Verbis Support

Claims 27-29 recite that the composition is an 'association' of granulocyte colony stimulating factor and placental growth factor. However, the specification is void of any literal support for the term 'association'.

Claims 30,32-36 recite that the method is for increasing the number of circulating while blood cells, circulating colony forming blood cells or circulating long term colony initiating blood cells in a patient in need thereof. However, the specification is void of any literal support for the specific patient population recited in claims 30,32-36. Claim 36 states that the administration is sequential or at intervals. However, the specification is void of any literal support for an administration that is sequential or at intervals.

Lack of Implicit or Inherent Support

Section 2163 of the MPEP states: 'While there is no in haec verba requirement, newly added claim limitations must be supported in the specification through express, implicit, or inherent disclosure'.

Claims 27-29,35 recite that the composition is an 'association' of granulocyte colony stimulating factor and placental growth factor. The dictionary definition for 'association' (from the internet site http://dictionary.reference.com/browse/association accessed 9/4/08) states that an association can be a connection or combination (definition 4) or can include a weak form of chemical bonding (definition 8). In the reply dated 5/28/08 (page 4) applicant states that the support for claims 27-29 can be found in page 1 paragraph 1 of the specification, the examples, and claims 3-4 as originally filed. The original disclosure supports a 'combined pharmaceutical preparation' (claim 1) and a 'combination of G-CSF and PlGF' (page 1 first paragraph). However, support for a 'combination' is not the same as support for an 'association'. As cited above, an association can be 'a connection'. In the instant case, an association of G-CSF and PlGF could be a fusion protein in which the proteins are connected via a linker. However, the specification does not provide support for such an association. One would not conclude that there

is support for instant claims 27-29. As cited above, an association can include specific types of chemical bonding. However, the instant specification supports a 'combination' which does not imply nor would it lead one to infer that there is some type of chemical bonding. Hence, it can not be said that the specification provides support for an 'association' of granulocyte colony stimulating factor and placental growth factor.

Claims 30,32-36 recite that the method is for increasing the number of circulating while blood cells, circulating colony forming blood cells or circulating long term colony initiating blood cells in a patient in need thereof. In the reply dated 5/28/08 (page 4) applicant states that the support for claims 30 can be found in claims 2-3 as originally filed. However, claims 2-3 as originally filed are drawn to compositions. A composition does not lead one to the specific patient population as recited in claims 30,32-36. Original claim 9 and the specification page 5 lines 11-17 recite specific patients such as those recited in instant claim 31 which is not included in this rejection. Although the patients described in instant claim 31 are recited in the specification, instant claim 30 and dependent claims 32-36 recite a much broader patient population – patients who are in need of increases in specific blood cells. It is noted that white blood cells and colony forming cells are recited in the specification as parameters evaluated (page 7 lines 8-12). However, a parameter that is evaluated is not the same as a specific patient population. One would not conclude that there is support for instant claims 30,32-36. Further, claim 36 states that the administration is sequential or at intervals. Although the specification (page 5 lines 18-20) provides support for simultaneous or separate administration, such statement does not lead one to administration at intervals. Hence, it can not be said that the specification

provides support for the patient population of claims 30,32-36 or the specific administration modes of claim 36.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 27-32,34-36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Robinson et al (In vivo v16 2002 pages 535-540 as cited previously) and Merck Manual (entry for neutropenia) and Hattori et al (Nature Medicine v8 2002 pages 841-849 as cited in IDS).

Robinson teach (abstract) the use of recombinant human granulocyte colony stimulating factor (G-CSF) to mobilize hematopoietic stem cells for use in transplantation and to treat neutropenia for example. Robinson does not define neutropenia. The Merck Manual (accessed

from http://www.merck.com/mmhe entry for neutropenia) teaches that neutropenia is an abnormally low number of neutrophils in the blood (first sentence). The Merck Manual teach that neutrophils are white blood cells (page 1 9th sentence). Thus, Robinson teach the patient population recited in claims 30,32-36 of the instant invention. The Merck Manual is cited to show a universal fact and definition and as such the date of the reference is not relevant (see MPEP section 2124). Robinson recognize that rapid clearance is a disadvantage of recombinant molecules and that a goal is to achieve clinical efficacy with fewer injections (abstract). Robinson teach (page 535 2nd column see also titles of reference 2) that G-CSF has been used in the clinic following chemotherapy thus meeting the patient population recited in claim 31 of the instant invention. Robinson teach (page 535 2nd column see also titles of references 5-7 on page 538) that G-CSF was administered to improve neutrophil recovery and significantly reduced the period of neutropenia.

Robinson does not expressly teach the use of G-CSF together with the use of placental growth factor.

Robinson recognize that rapid clearance is a disadvantage of recombinant molecules and that a goal is to achieve clinical efficacy with fewer injections (abstract). Thus one would be motivated to look for alternate strategies and techniques to achieve such a goal.

Hattori teach that placental growth factor (PlGF) augments the number of circulating hematopoietic cells and that the mobilization of hematopoietic cells followed the kinetics of placental growth factor plasma elevation (page 844 last paragraph to page 845 first paragraph and figure 4). Hattori teach that the studies suggest that PlGF which is endowed with a low toxicity profile provides a strategy to induce hematopoiesis after chemotherapy/radiation

(compare claim 31 of the instant invention), or in hematological disorders (page 842 first paragraph).

Robinson teach (abstract) the use of recombinant human granulocyte colony stimulating factor (G-CSF) to mobilize hematopoietic stem cells. The work of Hattori (page 844 last paragraph to page 845 first paragraph and figure 4) suggest that placental growth factor mobilize hematopoietic stem cells. As such, the prior art included both elements of the instantly claimed compositions: G-CSF and PlGF. One of skill in the art could have combined the elements as claimed by known methods with no change in their respective function (mobilize hematopoietic stem cells) and the combination would have yielded predictable results to one of ordinary skill in the art at the time of the invention.

Further, section 2144.06 of the MPEP states that it is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose in order to form a third composition. The idea of combining them logically flows from their having been individually taught in the prior art. Robinson teach (abstract) the use of recombinant human granulocyte colony stimulating factor (G-CSF) to mobilize hematopoietic stem cells. The work of Hattori (page 844 last paragraph to page 845 first paragraph and figure 4) suggest that placental growth factor mobilize hematopoietic stem cells. Therefore, the combination of G-CSF and PlGF to mobilize hematopoietic stem cells logically flows from their having been individually taught in the prior art.

Robinson teach (abstract) the use of recombinant human granulocyte colony stimulating factor (G-CSF) as recited in claim 27. Although Hattori does not expressly teach the use of the recombinant human PlGF it would have been obvious to use a recombinant and human version

of the molecule since such substitutions are well-known in the art. The substitution of one known element for another would have yielded predictable results to one of ordinary skill in the art at the time of the invention. As such, the limitations of claim 28 are met.

Since Robinson teach that the G-CSF can be administered by infusion or injection (abstract, page 535 2nd column) one would be motivated to formulate the G-CSF and PlGF combination in such forms thus meeting the limitations recited in claim 29. Further, it would have been obvious to administer the G-CSF and PlGF either separately in sequence or simultaneously since those are the typical well-known modes of administering combinations thus meeting the limitations recited in claims 32,34-36 of the instant invention.

It is noted that claim 27,35 recite that the composition is an 'association'. Since the composition is a combination of components the ingredients are necessarily associated (i.e. combined, compare dictionary definition used in 112 1st paragraph section).

It is noted that claim 27 states 'wherein said association is able to….'. Since the combination of Robinson and Hattori teach the combination recited in the instant claims the properties recited in the claims are necessarily present absence evidence to the contrary (see MPEP section 2112.01).

It is noted that claim 27 recited 'consisting essentially of'. Section 2111.03 of the MPEP states:

> The transitional phrase "consisting essentially of" limits the scope of a claim to the specified materials or steps "and those that do not materially affect the basic and novel characteristic(s)" of the claimed invention.
> For the purposes of searching for and applying prior art under 35 U.S.C. 102 and 103, absent a clear indication in the specification or claims of what the basic and novel characteristics actually are, "consisting essentially of" will be construed as equivalent to "comprising."

In the instant case, there is no clear indication in the specification or claims as to what the basic and novel characteristics are. Therefore, "consisting essentially of" will be construed as equivalent to "comprising".

Although unclear (see 112 2nd) for purposes of examination, claims 30-36 have been interpreted such that the claims are inclusive or open-ended and do not exclude additional method steps.

Claims 27-36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Robinson et al (In vivo v16 2002 pages 535-540 as cited previously) and Merck Manual (entry for neutropenia) and Hattori et al (Nature Medicine v8 2002 pages 841-849 as cited in IDS) and Anderlini et al (Journal of the American Society of Hematology v90 1997 page 903-908 as cited in IDS) and Carmeliet (US 7,105,168 as cited previously).

As discussed above, Robinson, Merck Manual, and Hattori render obvious claims 27-32,34-36.

Robinson, Merck Manual, and Hattori do not expressly recite the doses of claim 33.

It would have been obvious to one skilled in the art at the time of invention to determine all optimum and operable conditions (e.g.doses), because such conditions are art-recognized result-effective variables that are routinely determined and optimized in the art through routine experimentation. ("[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). *See* MPEP § 2145.05).

Anderlini teach that doses of, for example, 24 ug/kg/day (page 904 first column 16th line from the bottom) of recombinant human G-CSF have been used previously thus meeting the range as recited in claim 33 of the instant invention. Carmeliet teach PlGF (specifically human PlGF column 6 line 9) use as part of treatments such as for transplantations (column 3 line 22) and specifically teach that recombinant PlGF is used (column 15 line 7) and PlGF dosages 'of 15ug/kg/day of active ingredient up to 100 ug/kg/day or higher' (column 15 line 12) are deemed to be a safe level thus meeting the range as recited in claim 33 of the instant invention. Although the references do not necessarily teach G-CSF and PlGF for the identical use as in the instant invention, one of skill in the art would use the prior art doses as starting points for the routine optimization.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to RONALD T. NIEBAUER whose telephone number is (571)270-3059. The examiner can normally be reached on Monday-Thursday, 7:30am-5:00pm, alt. Friday, EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on 571-272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Ronald T Niebauer/
Examiner, Art Unit 1654

/Anish Gupta/
Primary Examiner, Art Unit 1654